# PATENT COOPERATION TREATY

# PCT



## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>DAB:ST:FP19199 | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>**PCT/AU2004/000253** | International filing date *(day/month/year)*<br>27 February 2004 | Priority date *(day/month/year)*<br>28 February 2003 |
| International Patent Classification (IPC) or national classification and IPC<br>**Int. Cl.**[7] C07D 235/10, 263/56, 317/50, 317/52, A61K 31/36, 31/4184, A61P 31/00, 31/04, 39/00. | | |
| Applicant<br>BIODIEM LTD et al | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - [X] Box No. I Basis of the report
   - [ ] Box No. II Priority
   - [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [ ] Box No. VII Certain defects in the international application
   - [ ] Box No. VIII Certain observations on the international application

| Date of submission of the demand<br>30 June 2004 | Date of completion of the report<br>24 September 2004 |
|---|---|
| Name and mailing address of the IPEA/AU<br>AUSTRALIAN PATENT OFFICE<br>PO BOX 200, WODEN ACT 2606, AUSTRALIA<br>E-mail address: pct@ipaustralia.gov.au<br>Facsimile No. (02) 6285 3929 | Authorized Officer<br>**FRANCES RODEN**<br>Telephone No. (02) 6283 2239 |

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000253

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1 (b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☐ the international application as originally filed/furnished

☒ the description:

pages **1-5, 8-25** as originally filed/furnished
pages* **6,7** received by this Authority on **13 September 2004** with the letter of 13 September 2004
pages* received by this Authority on with the letter of

☒ the claims:

pages **26, 30** as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **27-29** received by this Authority on **13 September 2004** with the letter of 13 September 2004
pages* received by this Authority on with the letter of

☒ the drawings:

pages **1/2, 2/2** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/000253

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims 1-25 | YES |
| | Claims | NO |
| Inventive step (IS) | Claims 1-25 | YES |
| | Claims | NO |
| Industrial applicability (IA) | Claims 1-25 | YES |
| | Claims | NO |

2. Citations and explanations (Rule 70.7)

The following documents were cited in the ISR:

D1 WO 2002/102789

D2 US 3962415

D3 Synthetic Communications, 1994, vol. 24(6), pages 819-832, R. P. K. Kodukulla et al

D4 US 4469703

D5 US 4463009

D6 WO 2000/021381

D7 The Veterinary Quarterly, 1987, vol. 9, no. 4, pages 309-320, H. L. Dupont et al

D8 US 4948782

Novelty

None of the above citations disclose a method of promoting growth using the compounds of formula I as claimed in the present application. Therefore all claims are novel over the cited prior art.

Inventive Step

D1 is the closest prior art. This document discloses the exact same compounds as those of the present application, which are used to treat microbial infections.

D2 describes 1,3-benzodioxoles for use as agents for stabilising insecticidal phosphoric esters when present in an insecticide evaporator. These compounds are stabilisers and not antimicrobial agents themselves.

D3 discloses compounds with antimicrobial activity that fall within the scope of the present claims, namely 2g and 4g.

D4 discloses compounds falling within the scope of those of formula I, see examples 12 and 38 of the citation. These compounds are used as antibacterial agents and fungicides.

D1, D3 and D4 therefore disclose compounds falling within the scope of general formula I, and their use as antimicrobial agents. The question is therefore whether a person skilled in the art would as a matter of routine have been led to use these compounds as growth promotors.

Continued on Supplemental Sheet....

**Supplemental Box**

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: V

D5 describes dialkyl 1-(2-pyridinylthio)-1,2-hydrazinedicarboxylate N-oxides as useful antimicrobial agents and especially as growth promotants in monogastric meat producing animals. The structure of these compounds is very different to those of the present application and a person skilled in the art would not therefore have been led to try the compounds of the present application as growth promotors in light of this document.

D6 discloses the use of two antimicrobial enzymes as an alternative to antibiotics in feeds for animals. Page 1 line 22 to page 2 line 1 states that the mode of action of the antibiotics on the improvement of growth and feed conversion ratio is not fully understood. Therefore this citation does not teach that growth promotion is directly associated with antimicrobial action. This document uses two enzymes which work in tandem, one breaks down the cell wall and the other generates a compound toxic to bacteria. The structure and mode of action of these enzymes is very different to the compounds of the present invention. Therefore in light of this document a person skilled in the art would not have been directly led to use the substituted nitrostyrene antimicrobial compounds of the present claims as growth promotors.

D7 describes the use of antimicrobial agents in animal feeds and states that they are used for three reasons: to prevent infectious diseases caused by bacteria or protozoa, to decrease the amount of feed needed and to increase the rate of weight gain. Page 213 states that the effects on growth by antimicrobials is not fully known. It concludes that the economic benefit of growth promotants in animal feed is not outweighed by the risk to human health of development of a resistant strain. While antimicrobials and in particular antibiotics are known to be used as growth promotors, there is nothing in this citation to suggest that the synthetic compounds of the present invention might be useful as growth promotors. An inventive step for all claims can therefore be acknowledged.

D8 discloses a feed composition containing an erythromycin derivative which has decreased or absent antimicrobial activity. This citation therefore teaches away from the present invention.

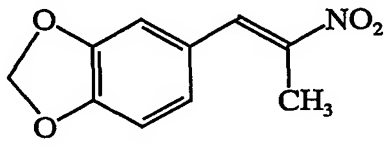
Industrial Applicability

All claims have industrial applicability.

alkyl.

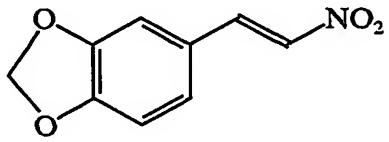
Specific examples of the compounds of the present invention are as follows:

(1) X and Y are O, $R_1$ is methyl and $R_2$ and $R_3$ are hydrogen (3,4-methylenedioxy-β-methyl-β-nitrostyrene)(hereinafter referred to as "Iksin")



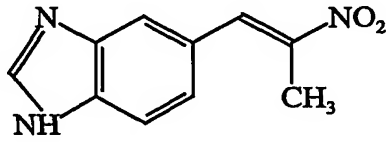
1

(2) X and Y are O and $R_1$ to $R_3$ are hydrogen (3,4-methylenedioxy-β-nitrostyrene)



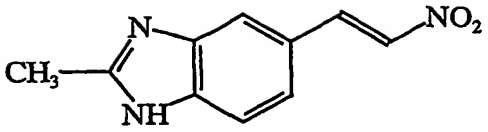
2

(3) X is N, Y is NH, $R_1$ is methyl and $R_2$ and $R_3$ are hydrogen (benzimidazole-5-β-nitropropylene)



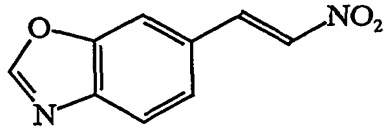
3

(4) X is N, Y is NH, $R_1$ is hydrogen, $R_2$ is methyl and $R_3$ is absent (2-methyl benzimidazole-5-β-nitroethylene)



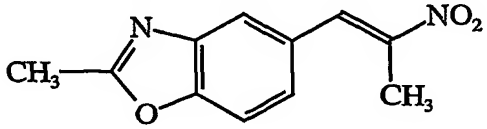
4

(5) X is O, Y is N, $R_1$ and $R_2$ are hydrogen and $R_3$ is absent (benzoxazole-5-β-nitroethylene)



5

(6) X is N, Y is O, $R_1$ and $R_2$ are methyl and $R_3$ is absent (2-methyl benzoxazole-5-β-nitropropylene)



6

By "pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, hydrate, ester, amide, active metabolite, analogue, residue or any other compound which is not biologically or otherwise undesirable and induces the desired pharmacological and/or physiological effect.

The salts of the compound of formula I are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts include salts of

mammal is a pig, cow or sheep and the bird is a chicken or turkey.

6. A method according to any one of claims 1 to 5, in which X and Y are either the same or different and selected from O and N.

7. A method according to claim 6, in which X and Y are both O.

8. A method according to any one of claims 1 to 7, in which $R_1$ and $R_2$ are either the same or different and selected from hydrogen, hydroxy, halogen and optionally substituted $C_{1-6}$ alkyl.

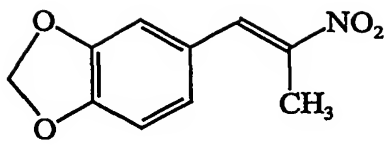
9. A method according to any one of claims 1 to 8, in which $R_3$ to $R_5$ are either the same or different and selected from hydrogen, hydroxy, halogen, nitro, $C_{1-6}$ alkoxy and optionally substituted $C_{1-6}$ alkyl.

10. A method according to claim 8 or claim 9, in which the halogen is chlorine or bromine.

11. A method according to any one of claims 1 to 10, in which the compound of the formula I is in the form of an E isomer.

12. A method according to any one of claims 1 to 11, in which X, Y,  , $R_6$ and $R_7$ are as defined in claim 1; $R_1$ and $R_2$ are either the same or different and selected from hydrogen, hydroxy, Cl, Br and $C_{1-4}$ alkyl; and $R_3$ to $R_5$ are either the same or different and selected from hydrogen, hydroxy, Cl, Br, nitro, $C_{1-4}$ alkoxy and $C_{1-4}$ alkyl.

13. A method according to any one of claims 1 to 12, in which X and Y are O, $R_1$ is methyl and $R_2$ and $R_3$ are hydrogen (3,4-methylenedioxy-β-methyl-β-nitrostyrene)



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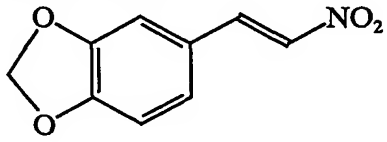
1

X and Y are O and $R_1$ to $R_3$ are hydrogen (3,4-methylenedioxy-β-nitrostyrene)



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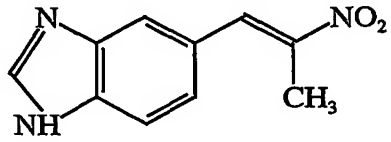
2

X is N, Y is NH, $R_1$ is methyl and $R_2$ and $R_3$ are hydrogen (benzimidazole-5-β-nitropropylene)



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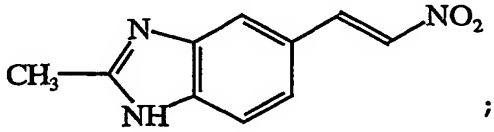
3

X is N, Y is NH, $R_1$ is hydrogen, $R_2$ is methyl and $R_3$ is absent (2-methyl benzimidazole-5-β-nitroethylene)



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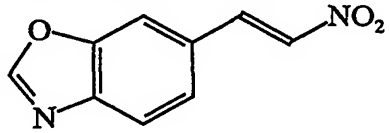
4

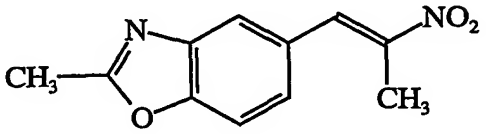
X is O, Y is N, $R_1$ and $R_2$ are hydrogen and $R_3$ is absent (benzoxazole-5-β-nitroethylene)



; or

5

X is N, Y is O, $R_1$ and $R_2$ are methyl and $R_3$ is absent (2-methyl benzoxazole-5-β-nitropropylene)



6

14. Use of the compound of formula I as defined in any one of claims 1 to 13 in promoting growth of a subject.

15. Use of the compound of formula I as defined in any one of claims 1 to 13 in the manufacture of a medicament or feed for promoting growth of a subject.

16. A compound of formula I as defined in any one of claims 1 to 13 for use in promoting growth of a subject.

17. A composition for promoting growth in a subject, which comprises the compound of formula I as defined in any one of claims 1 to 13 and a carrier.

18. A pharmaceutical or veterinary composition comprising the compound of formula I as defined in any one of claims 1 to 13 and a pharmaceutically or veterinarily acceptable carrier.

19. A composition according to claim 18 which is a topical, oral or parenteral composition.

20. A composition according to claim 18 or claim 19 in which the pharmaceutically or veterinarily acceptable carrier is an organic solvent.

21. A composition according to claim 20 in which the organic solvent is acetone, benzene, acetonitrile, DMSO or